EXHIBIT H-1

considerable credibility. Exploratory studies are considered interesting but need subsequent confirmation. Many QEEG studies are exploratory, and that substantially raises the threshold before accepting their findings.

Discriminant analysis is a technique to search for possible relationships in a large data set. Discriminant analysis is an exploratory technique that always finds some relationships. Many are irreproducible chance events. Some statisticians refer to discriminant analysis pejoratively as fishing expeditions. The high frequency of false positive relationships gives the discriminant analysis poor credibility. Two tactics have been proposed for overcoming the false positive problem. First, discriminant analysis can be used as an exploratory technique, and then follow up focused confirmatory testing is used to corroborate or disconfirm specific findings. Second, discriminant analysis should involve 10 times as many subjects as the number of features evaluated. QEEG easily produces hundreds or thousands of measured features. Many QEEG studies use discriminant analysis but fail to follow those precautions. That causes a great credibility problem for accepting their findings.

Independent replication has two possible meanings. First, it can refer to a second data set collected by the original investigators. For example in routine evoked potentials testing, a technician runs the test twice to see if it can be replicated. A different, second meaning of the term refers to a study's corroboration by separate, impartial investigators. When an investigator is commercially involved in a product under study, it is preferable to have others independently corroborate the claims—others without a commercial conflict or interest. Absence of such an independent corroboration raises the threshold before accepting the claims. Investigators with commercial conflicts of interest have published many QEEG reports. Without subsequent corroboration by impartial investigators, those claims have a credibility problem. Many QEEG claims about MTBI have such a problem.

Counterintuitive claims run contrary to well-established knowledge and theory. Such claims are difficult to understand and accept. For example, it is very unexpected that a QEEG mild head injury diagnostic discriminant's test accuracy is affected neither by drowsiness, nor sleep, nor by medications well known to affect EEGs (Thatcher et al., 1989, 1999). Most scientific advances move gradually from the known into the unknown. Incremental advances are more easily accepted, whereas novel unexpected leaps take a greater degree of demonstration. Counterintuitive claims substantially raise the credibility threshold before accepting those findings.

Marketing claims for QEEG diagnostic testing include its purported use as a diagnostic test for senile dementia, Alzheimer's disease, multi-infarct dementia, alcoholism, drug abuse, depression, bipolar disorder, schizophrenia, bulimia, violent behavior, headache, migraine, dyslexia, learning disorders, attention deficit disorder, Tourette's syndrome, Parkinson's disease, and sleep disorders. The community view of such promotions is one of skepticism. Separating the valid from the fanciful claim is needed. Indiscriminant marketing claims raise the credibility threshold.

Altogether, many QEEG claims are based on studies that have multiple drawbacks as mentioned above. Commercial QEEG marketing seems to have more difficulties than other areas of clinical neurophysiology. When assessing the claims that QEEG panels and discriminant analysis can diagnose brain injury from post-concussion syndrome and mild head injuries, one needs to be aware of the extent to which those studies have problems. Those problems need to be weighed when deciding how much credibility to give to the studies' conclusions.

4.2.4. Reproducibility and reliability

Reliability is defined by Thatcher et al. (2003b) as *reproducibility* or, 'the extent to which any measuring procedure yields the same results on repeated trials'. They note several studies that show repeatability of QEEG measurements. There is an important semantic issue here.

Reliability, as used in medical circles, is a very different from reproducibility. Physicians consider a diagnostic test as reliable when it usually gives a correct diagnostic result. Medically, a diagnostic test that, over and over again, gives the same erroneous or irrelevant result is reproducible but is not reliable.

Assessment of a test's reliability begins with the question, 'Reliable for what?' The reliability of a mild head injury QEEG panel or discriminant should be assessed among patients from the typical differential diagnosis of PCS complaints. To evaluate whether a test does reliably differentiate between depression and PCS, one would study several sets of patients with and without those disorders. This would be done also for other disorders on the differential diagnosis.

As an example of the latter issue, let us consider measurements of height. Growth hormone-producing pituitary tumors can cause people to grow tall. Let us assume that we have a tool that measures height with good accuracy and reproducibility. Does that mean that the tool reliably detects pituitary tumors? No, it does not. Some people are tall normally. Most tall people do not have a tumor. No matter how accurately and reproducibly one measures height, it is a poorly reliable predictor of pituitary tumors. Measurement reproducibility and diagnostic reliability are different.

Let us evaluate the literature on QEEG measurement reproducibility, particularly those reports that have been cited as evidence for QEEG's reliability as a diagnostic test for mild head injury.

Burgess and Gruzelier (1993) assessed topographic maps over a 40 min session. Topographic maps were difficult to reproduce especially in the delta band. The authors conclude that, '...the results indicate that reliability is insufficient to

allow topographic comparisons for a single individual...' They suggest that comparing one group to another group may be more reliable than for testing individuals. This study does not support the use of QEEG as a diagnostic test for MTBI.

Several studies mentioned below confirm that an individual's EEG absolute amplitude features remain reasonably stable over time when controlled well for the patient's state of alertness. These studies report that subjects with a tall alpha tended to have a tall alpha when tested again, and subjects with a small alpha tended still to have a small alpha, and such findings were reproducible over time.

Corsi-Cabrera et al. (1997) tested nine subjects during 11 sessions over 1 month. They used eight electrodes with bipolar reconstructions, and collected 10 two-second epochs per session, i.e. 20 s total per session. The median correlation coefficient across the 11 sessions was 0.94 for absolute amplitudes. Variability was greater for alpha and beta bands.

Lund et al. (1995) found that eight artifact-free eight-second epochs were sufficient to give a correlation coefficient around 0.9 for absolute power among 49 normal subjects and 44 schizophrenic patients.

Gasser et al. (1985) tested 26 children in 120 s recordings using 20 s epochs. The investigators measured absolute and relative power and autoregressive spectral peak parameters. Comparing two sessions run 10 months apart, EEG band correlation coefficients typically averaged 0.68. Results were similar for 20, 40 or 60 s EEG samples. These correlation coefficients show that slightly less than 50% of the typical QEEG measurements' variance is explained by within-subject reproducibility.

Salinsky et al. (1991) found absolute and relative power correlation coefficients of 0.84 between recordings made 12–16 weeks apart among 25 normal subjects. Absolute power was more reproducible than relative power, and total samples of 60 s were marginally more reproducible than 20 or 40 s.

Pollock et al. (1991) evaluated test–retest reproducibility of QEEG measurements in 46 normal controls. Retesting was at 20 weeks. For absolute amplitudes in theta, alpha and beta-1, correlation coefficients exceeded 0.6 at most electrode sites. Beta-2 correlations were somewhat lower. Delta did very poorly with almost no correlation coefficient above 0.60. For relative amplitudes, the correspondences were not so high, with only about 3/4 of the electrode sites exceeding 0.60 for theta, alpha and beta. Delta again did very poorly. The authors recommend using absolute amplitude rather than relative amplitude for clinical QEEG research.

These five studies show modest or good reproducibility for the simple absolute power or amplitude measurements when run by experts under controlled situations. The studies showed that absolute power or amplitude was more reproducible than relative power or amplitude measurements. Delta was the least reproducible band. Roughly half of the measurement variance was reproducible within subjects. The irreproducible half of the variance was due presumably to the usual normal moment-to-moment EEG fluctuations or technique variation between sittings.

Harmony and colleagues (Harmony et al., 1993; Fernández et al., 1993) assessed coherence in six subjects at rest and during cognitive tasks. Good correlation of the measurements was found between conditions within sessions. But between sessions the correlations were much lower even within subject within condition. Resting absolute and relative power measurements were more variable than coherences. Despite their baseline variability, they concluded that certain cognitive tasks, such as calculations, produced similar effects across subjects.

Arruda et al. (1996) applied principal components analysis (PCA) and factor analysis to QEEG recordings from 102 normal subjects during an auditory continuous performance task. The PCA solution was validated independently on 106 subjects. Seven components could account for 60–77% of the total experimental variance. This study differs from most QEEG or discriminant analysis paradigms, because in it involved only normal subjects, used principal components analysis and factor analysis, used an auditory performance paradigm. This is a theoretical study illustrating how such a mathematical technique might be applied to EEG. It does not test any research hypothesis or demonstrate usefulness for any clinical care issue.

QEEG clinical interpretation is plagued by false positives. Hamilton-Bruce et al. (1991) asked three different QEEG readers to process the same EEGs from 10 normal subjects. Each reader, or operator, selected 48 epochs, calculated a QEEG panel, and ran a general diagnostic discriminant. They found modest reproducibility among the QEEG panel measurements. They noted, however, '...between any two operators... there were a considerable number of statistically significant differences in the values for absolute power'. For the diagnostic discriminants, all three operators scored as 'normal' only two of 10 normal subjects. All three operators scored as 'abnormal' another two of 10 normal subjects. The other six normal subjects were given mixed or intermediate results. This discriminant result is an important one to keep in mind when assessing the accuracy of diagnostic discriminants in clinical care. Many false positive results occurred.

Some authors have suggested that these studies prove the reliability of QEEG panels and diagnostic discriminants. Those arguments are incorrect for several reasons. Many of these studies evaluated simple features like absolute amplitude, not the more complex ones usually included in QEEG. QEEG panels often employ more advanced features such as the ratios of amplitudes between sites, coherence, phase relationships, and complex combinations of features. Those are not well evaluated in the reproducibility studies mentioned above. Where they were assessed in these studies, the diagnostic discriminant faired poorly with far too many erroneous results.

Overall, these studies show measurement reproducibility, but they did not assess the QEEG's medical reliability as a diagnostic test. They do not show medical diagnostic reliability because they did not assess whether the measurements give correct medical diagnoses.

4.3. Problems with QEEG statistical normative comparisons

Many types of problems interfere with QEEG, especially for statistical normative comparison testing. The nonlinear, often abstruse nature of this process obscures many obvious errors, which then masquerade as possible abnormal results. Subtleties of these effects are difficult to understand even for persons who are experts in this field, and thus those not expert in EEG and QEEG clinical interpretation are easily led astray (Duffy et al., 1994; Nuwer, 1988, 1990, 1996).

Common problems are described below along with their potential impact on the use of QEEG for MTBI patients. See Table 3.

4.3.1. Artifacts, medications, state, and technical factors

Artifact contamination, drowsiness, anxiety, medication and technical factors can make a QEEG appear falsely abnormal.

Artifacts readily contaminate any EEG recording. Eyes, muscles, sweat, nearby equipment, poorly connected scalp electrodes, and many other sources generate these undesired signals. In QEEGs, they readily cause confusing patterns (Nuwer, 1987, 1988). Traditional artifact removal tactics can be insufficient for several reasons, such as artifact prevalence and subtlety, insufficient 'expert' training, failure to crosscheck findings, and recording too little EEG. Many QEEG recordings merge EEG and these contaminants, causing spurious results in frequency analysis, normative comparisons, discriminant analysis, and brain map findings.

Table 3
Factors that can lead to QEEG interpretation errors when using statistical normative comparisons

Technical
• Artifact contamination
• Drowsiness contamination
• Medication effects
• Filter changes
• Changes in electrode placement
Patient
• Drowsiness
• Anxiety
• Medication effects
Interpretation
• 'Different from average' does not necessarily mean 'diseased'
• Changes are not specific for particular disorders
• Some unusual EEG features are well known to have no clinical significance
Procedure
• Use of technicians to read the record and choose epochs
• Lack of safeguards and standards to prevent errors

Drowsiness occurs frequently in EEG recordings. Its decreased posterior alpha and generalized increased theta mimics brain damage. Slow rolling eye movements are important early signs of drowsiness (Santamaria and Chiappa, 1987). But many QEEG recordings fail to include the eye movement recording channels or 0.1 Hz low filter settings needed to detect those signs of early drowsiness. As a result, QEEGs can confuse early drowsiness with signs of brain damage.

Anxiety interferes with the resting state needed for the posterior alpha. Alpha biofeedback is used to train anxious patients to relax. The better they relax, the better their alpha amplitude.

Medications can change the EEG substantially. Benzodiazepines and barbiturates increase fast activity. Other medications cause slowing. Compared to control subjects on no medication, a patient on medications can have QEEG Z-score 'abnormalities' just due to medication effects. Such medications invalidate normative comparison techniques.

Electrode caps can be skewed or tilted, and cause an artificial asymmetry. Low filter settings can alter the EEG delta content. Such technical changes produce false abnormalities.

In routine traditional EEG reading, the professional reader is trained to identify and not to over-read these factors. These effects easily can be lost in the analysis of more abstract data in QEEG panels, brain maps and discriminant scores.

Overall, the effects of artifact contamination, drowsiness, medications, and unintended technical variations interfere with using statistical databases to detect EEG abnormalities.

4.3.2. Meaningless and non-specific changes

'Different' is not the same as 'diseased.' Computers can measure how one patient's EEG differs from an ideal average patient, but such a difference may be benign and of no medical significance. Metaphorically, some people are taller than average, other people are shorter than average, but this height difference is not necessarily due to a disease or a disorder. In QEEG measurements, this kind of a confusion frequently is seen. Some QEEG readers erroneously assume that any difference from average is due to disease. Really, though, different people often are simply different from each other.

Normal people have many QEEG statistical 'abnormalities,' so the concept of QEEG 'abnormality' becomes somewhat meaningless. QEEG panels measures hundreds or thousands of individual EEG features, each statistically transformed and tested. Statistics meant to test a few features are applied to enormous numbers of features, leading to many false positive 'abnormalities'. And these statistics have their own chance events; normal individuals may have a 2 to 18% false positive rate (Dolisi et al., 1990).

Table 4
QEEG panel reproducibility

# Features tested in each test panel	613
# Features abnormal in at least one test	237
# Abnormal features that were	
Abnormal in 1 of 4 tests	148/237(62%)
Abnormal in 2 of 4 tests	52/237(22%)
Abnormal in 3 of 4 tests	29/237(12%)
Abnormal in all 4 tests	8/237(3%)

A patient had the same QEEG panel performed on four separate occasions after a possible mild traumatic brain injury. The normal and abnormal features were counted for each of the four tests, and were compared across the tests. The data showed that most flagged abnormalities were not reproducible across the four tests. This illustrates the QEEG panel's reproducibility or lack thereof.

The QEEG, when measuring thousands of features, always flags some features as outside the normal range even in a normal healthy person.

Even an individual's results change over time. Table 4 presents the reproducibility of one patient's QEEG panel when tested on four occasions. While many features show up as 'abnormal' on these tests, the specific features vary considerably from test to test. That example shows how the detailed test results are more random or irreproducible.

Particular QEEG changes are non-specific. There are no pathognomonic changes. A variety of disorders can cause the same results (Coutin-Churchman et al., 2003; Mies et al., 1984). QEEG does not differentiate among diagnoses. A serious, common reading error is to attribute QEEG changes to a single specific diagnosis. Most real EEG or QEEG changes are non-specific.

Normal variants occur commonly in EEGs. Some occur rarely among normal people, but have no diagnostic significance. Available normative databases are insufficient for capturing the breadth of these non-diagnostic features.

In normative comparisons patient must be compared to his or her own age group, because EEG frequency content varies considerably with age. Consider a database with 625 normal subjects from age 2 months to 82 years (Thatcher et al., 2003a). Most of those subjects were children. Among adults, 24 subjects were 18–21 years old, 21 were 21–25 years old, 22 subjects in the group averaging 30 years of age, and 32 subjects in the older group averaging 57 years of age. This means that EEGs for most adults are compared to 21–32 normal control subjects of their own age group. That number is insufficient to account for the breadth of normal EEG patterns and known normal variant waveforms. Metaphorically, consider how accurately would the faces of two dozen people represent the breadth and variety of normal faces, especially if a thousand features were measured on each face.

Overall, meaninglessness or non-specific changes frequently occur, which interferes with using statistical databases to detect EEG abnormalities.

4.3.3. Who reviews the EEG and selects the epochs for analysis?

The QEEG user chooses epochs, or EEG segments, for analysis. The choice is critically important. Usually several dozen epochs are chosen, each several seconds long. Often about a minute of EEG is processed, sometimes representing 10% or less of the recorded EEG. Subjective selection can be very biased in choosing epochs, and this can highly influence the analysis. Widely varying findings result from different people processing from the identical EEGs (Hamilton-Bruce et al., 1991). 'Abnormal' results can be produced on normal person by selection bias. Truly abnormal findings can be missed by selectively eliminating them.

The skill, knowledge, ability, training, and experience of the person selecting epochs are very important. Unfortunately, even some well known labs leave the selection task to technicians. The senior lab professional does not examine the whole EEG from which the data were extracted (E. R. John, personal communication). Such a technician becomes the 'expert' who must identify artifacts and drowsiness, and choose features to include or exclude. But many technicians are insufficiently trained in the necessary neurological medical, diagnostic, and EEG interpretation skills. There are no standards in the field to prevent such procedures from creating erroneous results.

Sometimes, the professional clinician using QEEG is a speech pathologist, clinical psychologist, other allied health professional, or an unlicensed person. Such users generally lack sufficient skills, knowledge, ability, training, and experience needed to be expert in the necessary neurological medical, diagnostic, and EEG interpretation issues.

There are no generally accepted standards for QEEG processing. Proposed guidelines (Duffy et al., 1994) often are not followed and are not generally accepted. There are no clear safeguards against erroneous results. A variety of practitioners use these tools, some of whom have little or no training in EEG. Some QEEG labs fail to meet community standards for running and interpreting any EEG (American Electroencephalographic Society, 1994a,b,c,d). For example, too little EEG is recorded.

Even when careful processing has been carried out, there are no clear rules about interpretation. How many statistical hits are needed to deduce that something is truly abnormal? Does a reader really have to read the EEG tracing too? When do changes imply a particular diagnosis? What significance is attached to 'abnormal' results? These open questions have not been sufficiently answered.

Overall, a highly trained professional EEG reader should review the entire EEG record, select epochs, supervise the data processing, and provide the medical interpretations. The lack of accepted standards and safeguards leaves this field open to erroneous results.

4.4. Reports using QEEG in mild traumatic brain injury

4.4.1. QEEG features and panels

Several studies have evaluated QEEG panels in MTBI.

Von Bierbrauer et al. (1992) studied 31 patients within 24 h of a mild head injury. Reversible post-traumatic changes were found, with similar changes seen both in routine EEG and QEEG. They found abnormalities in 82% of patients at 24 h, 73% at 1 week, 50% at 3 weeks, and 32% at 2 months. Routine EEG alpha frequency increased from 9 to 10 Hz during the 2 months after the MTBI. QEEG show a similar increase from 9.3 to 10.0 Hz over those 2 months. See Fig. 1. The QEEG theta/alpha ratio dropped from 0.8 to 0.63 during this time. By 2 months most abnormalities were intermittent dysrhythmias, which were seen only in the routine EEG. This study after mild head injury show QEEG changes that resolved over several months. The most prominent change was a 0.7 Hz improvement in alpha peak frequency.

Watson et al. (1995) recorded QEEG in 26 young men admitted for mild closed-head injury. They were retested 10 days and 6 weeks later. QEEG theta–alpha ratios improved significantly in the first 10 days, and were

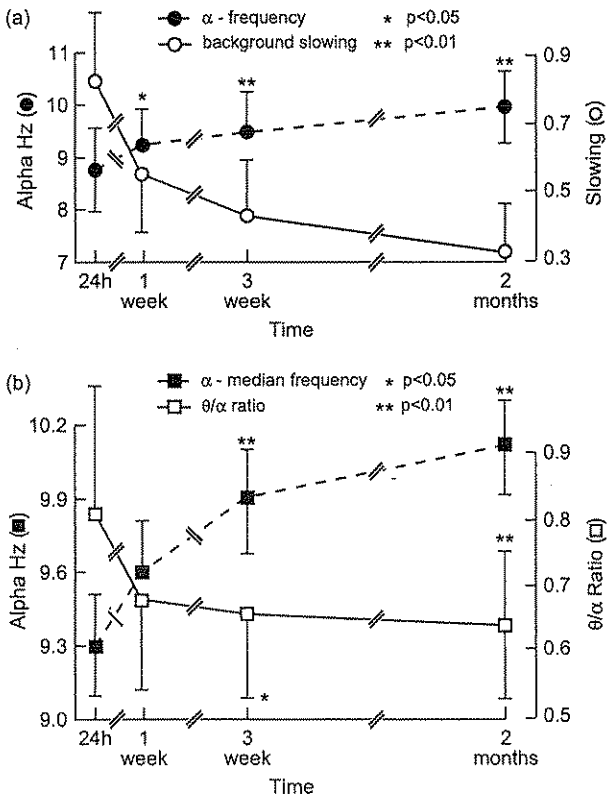

Fig. 1. Changes in EEG and QEEG were seen among 31 patients during the 2 months after a MTBI. (A) In routine EEG, the posterior dominant alpha frequency gradually increases and the amount of intermixed slowing gradually decreases. (B) In QEEG, the median posterior alpha frequency increases and the theta/alpha ratio decreases. Adapted from von Bierbrauer et al. (1992).

considered normal at 6 weeks. Slower QEEG improvement corresponded to greater the residual symptoms at 6 weeks. Residual left temporal EEG changes corresponded to complaints of cognitive symptoms 1 year after injury.

Tebano et al. (1988) assessed frequency analysis in 18 minor head injury patients compared to controls. They reported increased slow alpha (8–10 Hz) accompanied by reduced fast alpha (10–12 Hz) and reduced fast beta. They reported no change in total alpha, but they did see a decreased alpha mean frequency.

The Belfast head injury study also reported transient post-concussive increased theta frequency activity (Fenton et al., 1993; Montgomery et al., 1991; McClelland et al., 1994). That slowing disappeared over 6 weeks (Fenton, 1996) paralleling symptom resolution.

Coutin-Churchman et al. (2003) conducted QEEG panels in 67 normal subjects and 340 patients. Most had psychiatric disorders, such as depression or substance abuse. Others had migraine, closed head injury, or other various diagnoses. QEEG was read as abnormal in 83% of patients and 12% of the normal subjects. The most frequent abnormality was relatively decreased slow activity, which corresponded to MRI evidence of cortical atrophy. Increased beta was found with medications such as benzodiazepines. No QEEG features or patterns could differentiate among various diagnoses.

Korn et al. (2005) studied 17 patients with post-concussion syndrome. Many had suffered a mild closed head injury. Three had small intracerebral hemorrhagic contusions, and another had an epidural hematoma. QEEG showed increased slowing and decreased alpha. Brain CT and MRI revealed no focal abnormality. SPECT showed focal perfusion reduction in 85% of patients, and blood brain barrier breakdown in 73%. QEEG abnormalities were focal and varied in location. QEEG abnormality location corresponded to SPECT evidence of blood brain barrier breakdown. In eight patients with persistent post-concussion syndrome, focal EEG and SPECT abnormalities were in similar locations. In one patient the clinical syndrome, EEG and SPECT resolved in parallel. At least some PCS patients, the focal cortical impairment after head injury may be due to focal blood–brain barrier breakdown.

Haglund and Persson (1990) studied 47 former amateur boxers. Among them 22 had fought many matches and 25 had fought few matches. Investigators compared them to 25 soccer players plus 25 track and field athletes. There were more mild or moderate routine EEG changes among boxers than for other athletes. QEEG did not significantly differ among the groups.

Several other reports have been published about QEEG and mild head injury. Some are anecdotes (Mas et al., 1993). Others describe quantitative analysis of MRI T2 relaxation times (Thatcher et al., 1998a,b, 2001a). The latter are not demonstrations of clinical usefulness of QEEG in head injury, but this MRI work has made several interesting basic scientific observations. White matter T2 relaxation time

Table 5
QEEG findings after mild traumatic brain injury

Immediate reduction alpha mean frequency
Immediate increased theta/alpha ratio
Changes resolved over weeks to months
Improvement was associated with symptom resolution
Left temporal slowing or decrease fast activity may correspond to residual cognitive symptoms
Coherence did not correspond to outcome, disability, or diffuse axonal injury
Focal EEG changes may be accompanied by focal blood brain barrier breakdown
No consistent differences were seen between head injury, depression, or other diagnoses

correlated with increased frontal polar delta. Grey matter T2 relaxation time correlated with increased slow frequencies, a well-defined alpha peak frequency, and decreased left temporal alpha and beta amplitude. Longer T2 relaxation times corresponded to decreased EEG coherence for short interelectrode distances, and increased EEG coherence for long interelectrode distances. Changes in cognitive function corresponded to some of these findings.

Overall, several QEEG studies have been reported in MTBI. Their findings are listed in Table 5. QEEG may be useful as a research technique in the hands of highly expert users. But its high rate of false positive findings and the lack of diagnostic specificity preclude routine clinical usefulness.

4.4.2. Severe traumatic brain injury

Two studies of more severe head injuries deserve mention here because they provide background useful for the discussion of MTBI. Wirsén et al. (1992) recorded QEEG in 18 frontal trauma patients. Most had severe injuries. Neuroimaging tests showed obvious damage. Slowing seen in QEEG and routine EEG corresponded in general to lesion size, severity, regional blood flow, neuropsychological function, and outcome among the severe head trauma patients. The QEEG had localizing information among severe head injury patients, but it was the same information already available in standard neuroimaging techniques.

Kane et al. (1998) recorded QEEG in 60 comatose patients after severe closed head injury. Left central-temporal fast activity correlated with outcome and disability. Coherence did not correspond to outcome or disability. Diffuse axonal injury (DAI) at autopsy did not correspond to coherence measures. Interhemispheric coherence was significantly reduced during coma in general, except in the beta band. QEEG was no better as a prognostic tool than routine EEG reading. The lack of correlation between DAI and coherence for severe head injury raises caution about trying to relate coherence changes to DAI for MTBI.

4.4.3. Diagnostic discriminants

Diagnostic discriminants have been called highly sensitive, accurate tests for the diagnosis of PCS (Duff, 2004). Several studies have been cited to support that position as described below.

Thatcher et al. (1989) developed a head injury diagnostic discriminant. A diagnostic discriminant was derived based upon 264 mildly head injured patients and 83 controls. Twenty EEG features were identified, listed in Table 6. Fifteen of the 20 elements making up the discriminant are decreased posterior alpha and beta. They tested 608 mild head trauma patients and 108 normal subjects. Most patients were tested in a split-half replication that classified correctly about 90% of the patients. A false-positive rate around 10% was reported for normal controls. Some patients were tested several times, most with similar results upon retesting. In a follow-up study of 70 head injured patients at a separate site, over 90% of the patients were correctly classified. Effect of medications was considered not significant, but that assessment included all kinds of medications—not just those known to affect EEGs.

The role of short distance coherence remains to be clarified. The 1989 mild head injury discriminant reported that three short-distance coherence measures, the top three items in Table 6, were positively correlated head injury. In contrast, a follow up study (Thatcher et al., 1998b) indicated that short-distance EEG coherence was negatively correlated with its marker for head injury (lengthened MRI T2

Table 6
List of the 20 EEG features used in a mild head injury diagnostic discriminant function (Thatcher et al., 1989)

EEG feature	Correlation
Theta coherence between Fp1 and F3	0.3366
Beta coherence between T3 and T5	0.2598
Beta coherence between C3 and P3	0.3915
Beta phase lag between Fp2 and F4	−0.4658
Beta phase lag between F3 and F4	−0.4537
Alpha amplitude difference between F4 and T6	0.3298
Alpha amplitude difference between F8 and T6	0.3129
Alpha amplitude difference between F4 and T6	0.2886
Alpha amplitude difference between F8 and T6	0.2921
Alpha amplitude difference between F3 and O1	0.2939
Alpha amplitude difference between F4 and O2	0.3241
Alpha amplitude difference between F7 and O1	0.2944
Alpha amplitude difference between F4 and O2	0.2722
Alpha relative power for P3	−0.2612
Alpha relative power for P4	−0.2544
Alpha relative power for O1	−0.3532
Alpha relative power for O2	−0.3529
Alpha relative power for T4	−0.2390
Alpha relative power for T5	−0.2851
Alpha relative power for T6	−0.2832

Note this mild head injury diagnostic discriminant's heavy reliance on posterior alpha amplitude. Correlations show the direction and relative magnitude relationship between each feature and the discriminant function. For each listing of an alpha feature, a smaller posterior alpha corresponds to the discriminant function's diagnosis of head injury.

relaxation time) and reduced cognitive function. The two studies' opposite coherence results remain to be explained.

Thatcher also has noted that, 'the Department of Defense and Veterans Administrations specifically tested the effects of drowsiness even to the extent that patients were allowed to sleep and the QEEG discriminant function was not significantly affected' (R.W. Thatcher, personal communication). This counterintuitive point deserves further corroboration and publication of results.

Further questions and concerns remain. Corroboration would be helpful in light of the general shortcomings of discriminant analysis, especially given the split-half replication and subsequent commercialization. It is counterintuitive that the discriminant is unaffected by benzodiazepine medications. It remains to be tested on other disorders that cause cognitive complaints. How well does it apply to older or younger subjects? If indeed it is sensitive to decades-old mild head injuries, then how specific is it to the particular recent head injury in question? Can technicians identify useable EEG epochs in place of skilled professional electroencephalographers? The published study did not validate using a technician to choose epochs. The discriminant is based heavily on low amplitude posterior alpha, but that was shown previously in routine EEG to be a non-specific sign, often due just to anxiety, and not a reliable sign of mild head injury. Can the discriminant really diagnose mild head injury, or is it just a non-specific measure of low posterior alpha? Many of these issues were discussed at greater length above.

One good way to judge such a tool is to see how accurately it works in the hands of others. Two studies have assessed the Thatcher diagnostic discriminant. Trudeau et al. (1998) evaluated the Thatcher diagnostic discriminant in 43 veterans. One group had suffered from military blast concussions severe enough that others near them were killed or severely injured. Another group had non-military head injuries. The Thatcher discriminant was abnormal in 88% of those with military blast concussion injuries, but abnormal only in 25% of patients without a military blast injury. However, it showed no difference between persons with non-military head injuries and those without such injuries. Trudeau noted the small size of their study, and recommended further study to validate their findings. These investigators criticized the Thatcher et al. (1989) report in that it failed to control for the effects of psychoactive drugs.

Thornton (1999) tested the Thatcher head injury discriminant on 39 head injury patients and in normal subjects. It was positive in 81% of patients who had no significant loss of consciousness, and in 71% patients who did have a significant loss of consciousness. However, the Thatcher discriminant had a false positive rate of 52% on prospectively tested normal subjects. Such a high false positive rate raises serious questions about the diagnostic accuracy of this head injury discriminant.

Based on the available literature, and considering the remaining unresolved questions and problems about the Thatcher discriminant, one can reasonably conclude that more work is needed before considering it as a credible diagnostic tool. Contrary to marketing claims, it is reasonable to predict that the tool is actually sensitive to a variety of confounding factors, that it is abnormal also in other medical conditions, and that it has problems with false positives. Meanwhile, we should await corroboration from well-controlled clinical trials conducted by impartial investigators.

Other discriminant functions also have been described in the literature, but they too have not been corroborated. Von Bierbrauer et al. (1992) described their own new discriminant using 31 head injury patients. This retrospective jack-knife discriminant evaluation included 26 QEEG features such as alpha median frequency and relative theta. There has been no prospective validation of this discriminant.

Thornton (1999) also recorded a QEEG panel in 32 with mild brain injury and 52 normal subjects. He carried out a retrospective split-half assessment of his own high frequency frontal coherence head injury discriminant. The author recognized that use of 2945 variables could cause discriminant false positive problems, so that the study results were considered exploratory, preliminary and not definitive. Thornton (2003) tested a different 2945 feature QEEG panel in 56 normal subjects and 85 patients at 17 days to 27 years after mild head injury. Some patients and normal subjects were on medications. Subjects read and performed others tasks during recordings. This retrospective search found increased global or focal theta, decreased alpha, decreased coherences, and increased asymmetries in head injury patients. They looked for but did not confirm the increased coherence reported previously in head injury by Thatcher et al. (1989).

Thatcher et al. (2001a,b) report on a new EEG severity index for traumatic brain injury. The original 1989 Thatcher head injury diagnostic discriminant was not re-evaluated. The new severity index was developed using discriminant analysis among 40 patients with mild, 25 with moderate, and 43 with severe mild head injury at 15 days to 4 years after injury. An EEG discriminant score was given as a number 1 through 10. This severity index accurately separated mild from severe head injury patients among their evaluation group. Results were validated in 503 patients. No normal subjects were tested. Patients were on a variety of medications, which was reported as having no effect on the results. However, drugs known to affect EEG were not singled out for testing.

Commercial firms market diagnostic discriminants for MTBI. Some are based on the published studies mentioned above. Other different, unpublished proprietary software also have been marketed as tools to diagnose MTBI.

Overall, the discriminant functions described so far are interesting. But such complex formulas and studies still will

need better corroboration. Several of these reports are retrospective and exploratory. The Thatcher mild head injury discriminant makes counterintuitive claims and is commercially marketed, but not yet corroborated. It failed to show good accuracy when evaluated by Thornton, or when tested for civilian injuries by Trudeau. It is unknown what it shows in other disorders on the differential diagnosis. Issues remain unresolved.

4.4.4. QEEG panels and discriminants for diagnosis after mild traumatic brain injury?

What can we conclude? What QEEG measures are markers for MTBI? How specific are they for that diagnosis?

Is low amplitude alpha a marker for brain injury from MTBI? Several prominent QEEG studies use decreased posterior dominant rhythm amplitude as a marker for brain damage after mild head injury. But from routine EEG studies, we know that many factors cause low amplitude alpha, e.g. drowsiness and anxiety. Long ago Meyer-Mickeleit (1953) and Jung (1953) showed that low-voltage alpha EEG occurs in chronic head injury patients no more often than in the normal, healthy population. A higher incidence of low-voltage EEGs in subjects undergoing medical expert examinations was shown to be due to a state of anxiety and tense expectancy, also termed 'psychogenic suppression of the alpha rhythm' (Scherzer, 1966). More recently in mild head injury, Tebano et al. (1988) found a decrease in fast alpha (10–12 Hz) plus increase in slow alpha (8–10 Hz) resulting in no net change in total posterior alpha. As such, low amplitude posterior alpha remains an unverified hypothetical diagnostic marker for brain injury after a MTBI. The low amplitude alpha reported in some studies is more likely to be non-specific.

Are coherence changes markers for brain injury from MTBI? Short-distance coherences were reported as increased (Thatcher et al., 1989) or at other times decreased (Thatcher et al., 1998b) with mild head injury. Some studies suggested that certain coherence changes accompany diffuse axonal injury (DAI). Overall, no consistent set of coherence bands, changes, or sites of change has been specified as the sequellae from MTBI. One study found no relationship between coherence measurements and confirmed DAI patients (Kane et al., 1998). As such, coherence changes remain an unverified hypothetical diagnostic marker for brain injury after a MTBI. The coherence changes reported in some studies may be non-specific.

Accepted EEG changes after MTBI include slowing of the alpha frequency and increased theta. These changes usually disappear over several weeks to months after mild head injury (Fenton et al., 1993; Koufen and Dichgans, 1978; McClelland et al., 1994; Montgomery et al., 1991; von Bierbrauer et al., 1992; Watson et al., 1995). Over longer times, most of changes were intermittent dysrhythmias (von Bierbrauer et al., 1992) and epileptic spikes (Torres and Shapiro, 1961), kinds of abnormalities that are not detected well by QEEG.

Several published reviews, opinion, and editorials (Hughes and John, 1999; Hoffman et al., 1999; Thatcher et al., 1999, 2003b) advocate for the diagnostic value and reliability of QEEG panels and diagnostic discriminants for diagnosis of MTBI. Their published reasons for supporting the diagnostic value of QEEG include:

- Studies show independent validation of results.
- Studies show QEEG's reliability.
- QEEG is accepted as a test for organicity.
- QEEG is accepted for use in some conditions, therefore, it should be considered useful in mild head injury.
- The clinician makes the diagnosis, not the test.
- A good clinician can assure clean data.
- New literature shows QEEG's usefulness.
- Investigators' conflicts of interest should not be considered.
- Because the critics do not conduct this testing on patients, they are not in a position to criticize it.
- QEEG critics have not published research studies to show that QEEG is not useful.

The issues of independent validation and reliability are discussed above. There is a lack of prospective corroboration by impartial investigators, and many points have failed corroboration. Reliability and reproducibility are different; evidence of test–retest reproducibility does not prove reliability as a diagnostic tool. The other reasons concern the following issues:

4.4.4.1. QEEG is accepted as a test for organicity. Organicity refers to the biological changes in brain function that accompany or underlie brain disorders, sometimes referred to as organic brain damage. Routine EEG is a traditional method to detect organic brain damage, e.g. to separate depression from dementia. Certain QEEG techniques can aid in that differentiation especially for severe cases (Brenner et al., 1986). But one cannot generalize from EEG's use for dementia to all other clinical scenarios and techniques. Different circumstances, such as the MTBI discussed here, and different techniques require their own evaluation.

4.4.4.2. The clinician makes the diagnosis, not the test. Diagnostic discriminants distort the clinical diagnostic process when they make automated statements such as, 'These results support the diagnosis of MTBI with a probability more than 95%'. Such a statement skews the process of diagnosis by inappropriately emphasizing one hypothesis and failing to acknowledge the flaws and non-specific nature of QEEG results. Also, too often QEEG users claim to have made the diagnosis because that is what the test found. In that way, users treat the test results as if it makes a diagnosis.

4.4.4.3. A good clinician can assure clean data. A trained EEG professional can prevent or can be aware of the introduction of drowsiness, artifact or other problems into a QEEG. But this is defeated when the clinical QEEG record review and epoch selection is delegated to a technician.

4.4.4.4. New literature shows QEEG's usefulness. The literature of research reports in peer-reviewed journals is reviewed above. A number of reports are retrospective or exploratory techniques without prospective validation. Others are conducted by investigators with financial conflicts of interest and not corroborated by impartial investigators. Other publications cited as supportive of QEEG's clinical usefulness in MTBI patients are just abstracts, anecdotes, opinions, reviews, methodology descriptions, or studies on severe head injury (for example, Hoffman et al., 1995, 1996a,b, 1999; Hughes and John, 1999; Mas et al., 1993; Sullivan et al., 1994; Thatcher et al., 1999).

4.4.4.5. Investigators' conflicts of interest should not be considered. Because the critics do not conduct this testing on patients, they are not in a position to criticize it. The medical community does consider financial conflicts of interest and a tool's reputation among the clinical community as important issues to be considered in deciding a study's credibility and a technique's utility. Physicians have a healthy skepticism for vendors and their spokespersons who promote new techniques or medications. Training programs teach young physicians to evaluate carefully claims of usefulness. This is rooted in the physicians' responsibility to be a careful steward of health care resources, and to use medications and diagnostics that are safe and effective. QEEG should not be granted an exception to careful professional assessment.

4.4.4.6. QEEG critics have not published research studies to show that QEEG is not useful. The burden is on the technique's proposers to show that their techniques are useful, not on the general community to disprove each claim.

4.4.4.7. How can we go forward from here?. Overall, QEEG still needs corroboration of its diagnostic usefulness. Corroboration should include rigorous, well-designed, well-controlled, prospective trials corroborating the existing proposals, and run by investigators without a commercial conflict of interest. Such a trial should include patients with other diagnoses from the differential of cognitive complaints seen after MTBI, and should run controlled studies of the effects of benzodiazepines, other medications, drowsiness and sleep on the diagnostic accuracy of the proposed tool. This common standard is used widely to evaluate proposed new drugs. The proposed use of QEEG as a diagnostic test for MTBI should meet the same standards.

5. Summary

MTBI is encountered commonly today in the general population. Various theories have attempted to explain the loss of consciousness. A massive neuronal discharge might produce a clinical state analogous to a non-convulsive epileptic seizure with post-ictal confusion. Mechanical forces produce two types of cellular damage. Ion leaks through cell membranes produce a temporary biochemical imbalance, which can trigger a spreading depression that could cause early amnesia or cognitive disturbances. Intracellular neurofilaments are misaligned which disrupts axoplasmic flow. Either process could cause long-term impairment and secondary injury. Some patients complain of persistent cognitive difficulties for weeks to months after such an injury. About 15% of patients continue to complain of symptoms a year after their injury. The nature of those persistent complaints is unclear.

EEG immediately shows initial epileptiform activity, followed by suppressed cortical activity lasting from seconds to about a minute. Many patients' EEGs return to normal within an hour. Others continue to show focal or generalized slowing that may last for weeks to a few months. The posterior alpha frequency is slower by an average of 0.7 Hz, gradually returning to baseline frequency over weeks to a few months. By 2 months, any residual EEG abnormality usually was an intermittent slowing. In the long run, the only EEG abnormalities that increased over time were epileptic spikes. Many EEG changes were subtle, often within the broad range of findings in the normal population.

EEG abnormalities are more common than clinical symptoms in the initial months after a MTBI. Patients with an abnormal exam generally have an abnormal EEG, although many more EEG abnormalities are subclinical. Later after the injury, there is poor correspondence between EEG and clinical signs, symptoms, imaging results or psychometric tests. EEG abnormalities are seen with some sports injuries, but those findings do not usually correspond to clinical findings. Decreased posterior alpha long after injury is more likely due to anxiety rather than brain damage. EEG does not predict, confirm, or measure PCS or PPCS, nor should mild EEG abnormality be used to substantiate an objective clinical brain injury. Nor can a normal EEG exclude an initial significant brain injury.

QEEG testing also shows the immediate reduction in alpha mean frequency and increase in theta slow activity, changes that usually resolved over weeks to months. Improvement was associated with symptom resolution. Left temporal slowing or decrease fast activity corresponded to residual cognitive symptoms in one study. Coherence did not correspond to outcome, disability, or diffuse axonal injury. No consistent differences separated

head injury from depression or other diagnoses. The low amplitude alpha and coherence changes, as reported in some QEEG panels and diagnostic discriminants, may be non-specific findings attributable to many possible causes.

QEEG diagnostic discriminant testing reports and commercial marketing make claims that they can identify MTBI. The Thatcher mild head injury discriminant makes counterintuitive claims that the EEG changes are unaffected by drowsiness, sleep, or medications well known to affect EEG. That diagnostic discriminant failed to show good accuracy when evaluated by Thornton or in civilian injuries tested by Trudeau. Other diagnostic discriminants have been reported, but have not been prospectively verified. It is unknown what these various diagnostic discriminants will show when used on patients with other disorders on the differential diagnosis of cognitive or emotional problems. These claims still need impartial corroboration and prospective validation.

QEEG panels and diagnostic discriminants still have many unresolved problems. These include the effects of artifact contamination, drowsiness, medications, and technical changes. Some 'abnormalities' actually are meaningless and non-specific distinctions from normal. False positive rates can be high, even greater than 50% among normal persons. Unqualified individuals sometimes analyze the records, select portions for review, or even render the professional interpretation. There are no generally accepted safeguards and standards. Some investigators had a financial conflict of interest. This and other factors raise the credibility threshold for accepting the results. Other factors include notable past failures of QEEG diagnostic testing, suboptimal study design (e.g. discriminant analysis, split-half replications, jack-knifing), failure to follow up with prospective validation, counterintuitive changes, and over-marketing of QEEG's usefulness.

Overall, the disadvantages of QEEG panels and diagnostic discriminants presently outweigh the advantages of those studies for the diagnosis of MTBI. More well designed prospective studies are needed. Diagnostic QEEG users need to remedy the procedural shortcomings.

EEG studies, quantitative or routine, remain a good physiological research tool for a better scientific understanding of MTBI. By continuing to improve our understanding of the pathophysiology of mild head injury, one can hope to identify the critical causes of injury, especially any secondary causes of injury that may unfold over days or weeks. These may lead to better future treatments for concussion to reduce PCS and reduce the likelihood of PPCS. Already, the knowledge and tentative scientific understanding of the second injury syndrome helps to guide public policy for prevention of subsequent greater injury. Further scientific work still is needed to pursue these goals of understanding better the pathophysiology, as well as to clarify how EEG can assist in the care of patients who have sustained a MTBI.

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